Mechanisms Regulating Feed Intake, Energy Expenditure, and Body Weight in Poultry[1,2]

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ABSTRACT To achieve energy balance and maintain a constant BW, changes in feed intake and energy expenditure must be coordinated and tightly regulated. This may not hold true for some poultry species intensively selected for such economically important traits as growth and meat production. For example, the modern commercial broiler breeder does not adequately control voluntary feed intake to meet its energy requirements and maintain energy balance. As a consequence, feeding must be limited in these birds to avoid overconsumption and excessive fattening during production. It is important to determine a genetic basis to help explain this situation and to offer potential strategies for producing more efficient poultry. This review summarizes what is currently known about the control of feed intake and energy expenditure at the gene level in birds. Highly integrated regulatory systems have been identified that link the control of feeding with the sensing of energy status. How such systems function in poultry is currently being explored. One example recently identified in chickens is the adenosine monophosphate-activated protein kinase pathway that links energy sensing with modulation of metabolic activity to maintain energy homeostasis at the cellular level. In the hypothalamus, this same pathway may also play an important role in regulating feed intake and energy expenditure commensurate with perceived whole body energy needs. Genes encoding key regulatory factors such as hormones, neuropeptides, receptors, enzymes, and transcription factors produce the molecular components that make up intricate and interconnected neural, endocrine, and metabolic pathway networks linking peripheral tissues with the central nervous system. Moreover, coordinate expression of specific gene groups can establish functional pathways that respond to and are regulated by such factors as hormones, nutrients, and metabolites. Thus, with a better understanding of the genetic and molecular basis for regulating feed intake and energy expenditure in birds important progress can be made in developing, evaluating, and managing more efficient commercial poultry lines.

Key words: feed intake, energy balance, appetite, adenosine monophosphate-activated protein kinase, regulation

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INTRODUCTION

Poultry breeders have intensively selected meat-type birds over many generations with specific emphasis on increasing growth rate (BW) and meat production. Increased body size in commercial chicken and turkey lines has been accompanied by unintended changes in correlated traits such as increases in voluntary feed intake and energy storage. Commercial broiler breeder strains, selected for rapid growth and high meat yields, do not adequately regulate voluntary feed intake commensurate with their energy needs. Consequently, these birds must be given a limited amount of feed to avoid overconsumption that can lead to excessive accumulation of energy stores (fat tissue), an undesirable BW and body composition, and a series of health-related complications (i.e., leg problems, reduced reproductive efficiency, etc.). Therefore, it is important to understand the regulation of feed intake and energy balance in birds to develop and better manage commercial lines of poultry.

In poultry species, as in all animals, BW is maintained throughout the lifecycle by adjustments to feed intake and energy expenditure. Both of these processes are controlled by complex and interconnected neuronal and endocrine networks that function to achieve energy homeostasis and maintain BW. Specific mechanisms have evolved to sense nutritional (energy) status. These are coupled with unique signaling pathways that link peripheral tissues with the central nervous system (**CNS**). Within the CNS, hypothalamic neural circuits play a critical role in integrating peripheral signals conveying information about energy and nutrient status, which is

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Table 1. Peptide signals associated with the regulation of feed intake and energy expenditure in birds[1]

Orexigenic (anabolic)	No effect	Anorexigenic (catabolic)
Neuropeptide Y	Melanin concentrating hormone	α-Melanocyte stimulating hormone
Agouti-related peptide	Orexins (A&B)	Growth hormone releasing factor
Peptide YY	Galanin	Corticotropin releasing factor
Pancreatic polypeptide	Motilin	Cocaine- and amphetamine-regulated transcript
		Leptin
		Ghrelin
		Glucagon-like peptide 1
		Cholecystokinin
		Bombesin
		Gastrin
		Urotensin I/Urocortin
		Neuromedin U/S

[1]Based in part on data reported by Furuse (2002) and Richards (2003).

interpreted and used to modulate feeding behavior and energy expenditure to maintain BW and energy stores at a set level.

There have been a number of reviews regarding the regulation of feed intake by CNS and peripheral tissue mechanisms in poultry (Sykes, 1983; Denbow, 1994; Kuenzel, 1994; Kuenzel et al., 1999; Furuse, 2002; Richards, 2003). However, our understanding of the mechanisms that integrate feed intake regulation with control of energy expenditure in poultry remains quite limited, especially concerning the genetic and molecular basis for this regulation. Because feeding behavior and energy homeostasis are basic processes crucial to the survival of all animals, it is logical to assume that the regulatory mechanisms governing these processes in birds and mammals would involve highly conserved neural and endocrine signaling networks as well as similar neuroanatomical sites (Kuenzel, 1994; Kuenzel et al., 1999). In fact, much of what has been discovered recently concerning the genetic basis for the mechanisms regulating appetite and energy expenditure has emerged from studies involving mammalian species. The purpose of this review is to discuss the regulation of feed intake and energy expenditure in poultry including recent genetic and molecular discoveries and some newly emerging concepts.

SIGNALING PATHWAYS

A wide array of signaling molecules that convey information about whole-body nutritional status have been identified and studied. Included among these are neuropeptides, hormones, nutrients, and metabolites produced by peripheral and CNS tissues in response to changes in nutrition and environment. For each of these signaling molecules to be active, specific sensors that recognize and bind them must be produced at sites of action. Sensors can be molecules such as transmembrane receptors, enzymes, transcription factors, and transporters. Together, each signal and its cognate sensor form a signaling pathway that can produce localized effects within individual cells and tissues or can act globally on the whole animal level.

Table 1 lists a number of peptides that have been studied in poultry with respect to their effects on feed intake. These signaling molecules function in peripheral or CNS sites, or both, to activate specific neural circuits or serve as endocrine and metabolic modulators that ultimately affect feed intake and energy homeostasis. Specific examples of some well-studied avian signaling molecules include neuropeptide Y (**NPY**), proopiomelanocortin (**POMC**) and its processed product alpha-melanocyte stimulating hormone (**αMSH**), cholecystokinin, and bombesin (Denbow, 1994; Kuenzel, 1994; Jensen, 2001; Furuse, 2002). It is clear that, despite the generally conserved nature of these peptide-signaling molecules in birds and mammals, there are differences in the function of specific peptide signals. For example, peptide YY and pancreatic polypeptide suppress appetite in mammals, whereas they are potent orexigenic agents in birds (Kuenzel et al., 1987; Ando et al., 2001). Although ghrelin stimulates feeding in mammals, it has been found to be anorexigenic in birds (Furuse et al., 2001; Kaiya et al., 2002; Saito et al., 2002, 2005; Geelissen et al., 2005). On the other hand, melanin concentrating hormone, orexins (A and B), galanin, and motilin all are potent orexigenic agents in mammals but are without any apparent effect on feed intake in chickens (Furuse et al., 1999; Ando et al., 2000; Furuse, 2002; Ohkubo et al., 2002). Thus, the fact that birds and mammals utilize common signaling molecules does not necessarily mean that they also share a common function.

A number of receptors have been identified and characterized in poultry species either at the gene or the protein level, or both, in peripheral and CNS tissue sites. Some prominent examples include the leptin receptor (Horev et al., 2000; Ohkubo et al., 2000; Richards and Poch, 2003; Liu et al., 2007), NPY receptors (Salaneck et al., 2000; Holmberg et al., 2002; Lundell et al., 2002; Bromee et al., 2006), melanocortin receptors (Takeuchi and Takahashi, 1998; Boswell and Takeuchi, 2005), the ghrelin receptor also known as the growth hormone secretagogue receptor (**GHS-R**; Tanaka et al., 2003; Geelissen et al., 2003), and adiponectin receptors (Ramachandran et al., 2006). It is important to note that with the exception of the leptin receptor, all of the examples of receptors cited above are members of the G protein coupled-receptor (**GPCR**) family. In fact, it has recently been reported that over 40 GPCR are linked to the regulation

of BW as members of signaling pathways that affect feeding behavior and energy expenditure (Schioth, 2006). Therefore, a better understanding of the structure, expression, and function of corresponding avian GPCR genes is essential to understanding their unique role(s) in regulating feed intake and energy expenditure in poultry. Using a homology-based approach with comparisons of all known human GPCR to chicken genome sequence, Lagerstrom et al. (2006) have detected and verified a total of 557 chicken GPCR genes that can be studied for differences and similarities with mammalian orthologs.

In the following text, 2 signaling molecules, ghrelin and leptin, are discussed in greater detail to illustrate examples of specific signaling axes. The gut-brain axis involves communication of information about the presence or absence of feed or specific nutrients in the gut to the brain and ghrelin falls into this category. The connection between adipose tissue (fat) and the brain involves communication of the level of peripheral tissue energy storage to the CNS, and leptin exemplifies this form of signaling.

Ghrelin, a peptide hormone produced by the stomach, has been reported to stimulate feeding in mammals (Wren et al., 2000). In birds, ghrelin is produced by the proventriculus, and it modulates feeding behavior in addition to functioning as a potent pituitary releasing factor for growth hormone mediated through the GHS-R (Furuse et al., 2001; Ahmed and Harvey, 2002; Kaiya et al., 2002; Baudet and Harvey, 2003; Wada et al., 2003). Interestingly, ghrelin has been shown to inhibit feed intake when administered centrally to chickens (Furuse et al., 2001; Saito et al., 2002). Ghrelin genes have been identified and characterized in chickens and turkeys (Kaiya et al., 2002; Richards et al., 2006). The predicted amino acid sequence of ghrelin in birds shows significant conservation especially in the amino-terminal region of the mature peptide hormone that contains an important site (serine 3) that is modified by esterification with a fatty acid (Kaiya et al., 2002). Expression and tissue localization of GHS-R transcripts have been reported in chickens and the widespread expression of the receptor is consistent with potential pleotropic effects of ghrelin (Tanaka et al., 2003; Geelissen et al., 2003, Richards et al., 2006). The discrepancy in function between avian and mammalian ghrelin peptides with respect to feed intake regulation is not readily apparent from the structure of ghrelin or its receptor (gene or protein). However, it has recently been reported that the inhibitory effect of ghrelin on feed intake in chickens may be mediated by the corticotrophin-releasing factor (**CRF**) system in the hypothalamus which is known to suppress feed intake (Saito et al., 2005).

Recently, it was reported that the preproghrelin precursor molecule in rats contained an additional 23 amino acid peptide hormone molecule that was named obestatin (Zhang et al., 2005). Obestatin, unlike ghrelin, was found to inhibit feed intake and decrease BW in rats. Like ghrelin which requires an amino-terminal fatty acylation modification for bioactivity, obestatin has been reported to require a carboxy-terminal modification (amidation) to bind to the orphan receptor GPR39, a member of the GPCR family (Zhang et al., 2005). However, subsequent investigations by a number of groups have failed to find any effect of obestatin on feed intake, BW, body composition, energy expenditure, or hypothalamic neuropeptides involved in energy balance regulation in rodents following central or peripheral administration of the hormone (Nogueiras et al., 2007). Moreover, it has recently been reported that obestatin does not bind to GPR39 or activate GPR39 signaling as originally indicated (Lauwers et al., 2006; Holst et al., 2007). Finally, targeted disruption of the GPR39 gene in mice had no effect on feed intake or BW (Tremblay et al., 2007). Together, these recent findings cast doubt on the role of the obestatin/GPR39 system in the regulation of BW and energy balance (Nogueiras et al., 2007).

Figure 1 shows different avian preproghrelins and demonstrates the presence of the 2 regulatory peptides (ghrelin and obestatin) derived from the same precursor in the chicken, turkey, duck and goose. There is uncertainty surrounding the posttranslational amidation of avain obestatin peptides because they all lack a terminal glycine residue that is highly conserved in mammalian obestatin peptides and required for carboxy-terminal amidation (Zhang et al., 2005). The chicken GPR39 gene has now been identified on chromosome 7 and, like its mammalian counterpart, codes for a protein that is a GPCR. The GPR39 gene is widely expressed in broiler chickens, in peripheral and CNS (including the hypothalamus) tissue sites (M. Proszkowiec-Weglarz and M. P. Richards, unpublished findings). Nothing is currently known about the role, if any, of the avian obestatin/GPR39 system in regulating feed intake and BW in birds or if it produces effects opposite those of ghrelin (i.e., stimulates feed intake and BW gain) as would be predicted from mammalian findings (Zhang et al., 2005). However, in light of the recent evidence obtained from mammalian models, it is entirely possible that this system will have no role in energy balance and BW regulation in birds. Perhaps, further study of the avian preproghrelin precursor and the 2 peptides derived from it will provide some additional insight into a possible function for the obestatin peptide and any unique physiological role(s) that it might play specifically in birds.

Although there is considerable evidence that strongly suggests a conserved role for leptin and its receptor in regulating BW and energy expenditure across many different mammalian species (Friedman and Halaas, 1998; Friedman, 2002), much less is known about avian leptin and its potential function(s). There have been 2 reports of the cloning and sequencing of a chicken leptin gene, and the predicted amino acid sequence shows high homology with mammalian (mouse) leptin proteins (Taouis et al., 1998; Ashwell et al., 1999). Despite these initial findings, considerable doubt has been cast on the validity of the gene sequence reported for chicken leptin and on reports of leptin gene expression in avian species

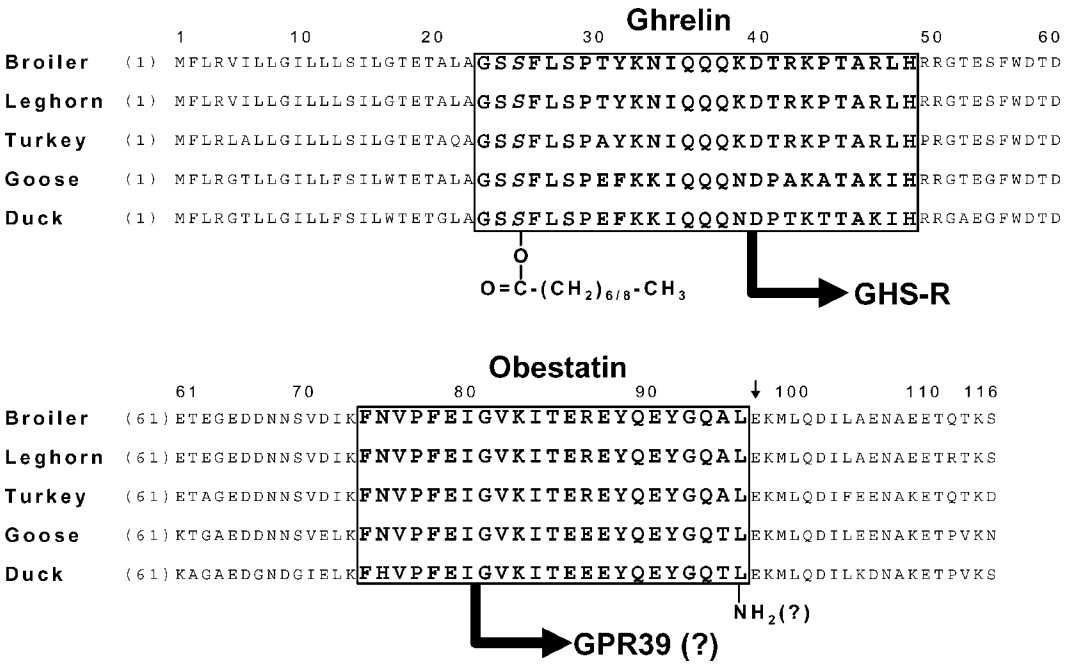

Figure 1. Amino acid comparisons of preproghrelin precursor proteins for different avian species. The locations of the mature ghrelin peptide and the putative obestatin peptide are indicated by boxing. The site within the mature ghrelin peptide (serine 3) for acylation by n-octanoic acid or n-decanoic acid required for ghrelin receptor (GHS-R) binding is indicated. Also, the proposed site of amidation (-NH_2) for obestatin required for binding to GPR39, the putative receptor for obestatin, is indicated. ↓ denotes the site of a terminal glycine residue (G), conserved in all mammalian obestatin peptides, that is changed to a glutamic acid residue (E) in avian peptides. GPR39 (?) denotes the current uncertainty concerning the binding and activation by obestatin of the orphan G protein-coupled receptor, GPR39. Amino acid sequences shown for broiler, White Leghorn, turkey, goose, and duck preproghrelin precursor proteins were obtained from GenBank accession No. BAC24980, AAP56234, AAP93133, AAQ56122, and AAQ56123, respectively.

(Friedman-Einat et al., 1999; Amills et al., 2003). Furthermore, an initial report of mapping the chicken leptin gene to a microchromosome (Pitel et al., 1999) was later determined to be incorrect (Pitel et al., 2000). A search of the draft sequence of the chicken genome also fails to indicate the existence of sequence corresponding to that reported for the chicken leptin gene. Thus, it appears likely that a leptin gene has yet to be cloned for chickens or any avian species. It is relevant to point out that leptin genes have recently been identified for some nonmammalian species including salamander, pufferfish, and frog that are markedly different from mammalian homologues (Kurokawa et al., 2005; Boswell et al., 2006; Crespi and Denver, 2006). This may also prove to be the case for avian leptin genes, although that remains to be determined. Despite low amino acid sequence homology in nonmammalian as compared with mammalian leptins, a common feature linking all leptin proteins appears to be a highly conserved tertiary structure (Crespi and Denver, 2006). This could explain the ability to detect leptin protein in plasma and tissue (liver and fat) samples from birds by immunoassay despite the inability to conclusively identify an avian leptin gene (Dridi et al., 2000b; Richards et al., 2000; Taouis et al., 2001; Kochan et al., 2006). Moreover, exogenously administered leptin is bioactive in avian systems. Peripheral and central administration of recombinant chicken or mammalian leptin proteins to birds reduced feed intake in some trials (Dridi et al., 2000a, 2005; Denbow et al., 2000; Taouis et al., 2001; Lohmus et al., 2003; Cassy et al., 2004) or was without effect in others (Bungo et al., 1999). The effect of administered leptin on feed intake may be influenced by the age and strain of the bird (Cassy et al., 2004). Moreover, it has recently been suggested that chickens with high growth rates (broilers) may be less sensitive or responsive to peripheral leptin levels than chickens with low growth rates (layers), indicating that the more rapid growth rate of broiler chicks may be related to a lower response (i.e., resistance) to anorexigenic signals from peripheral tissues (Cassy et al., 2004). Finally, immunization against leptin in chickens was found to mimic the loss of leptin bioactivity leading to increased feed intake, weight gain, and fat deposition (Shi et al., 2006). Thus, it appears that leptin is an anorexigenic factor that signals energy status in birds in a similar manner to its well-documented effects in mammals.

Leptin receptor genes have been cloned and sequenced for chickens and turkeys (Horev et al., 2000; Ohkubo et al., 2000; Richards and Poch, 2003; Liu et al., 2007). Based on the deduced amino acid sequence, it appears that the avian leptin receptor is quite similar to the mammalian receptor in its structure and binding properties. In addition, short form gene transcripts (coding for proteins truncated at their carboxy-terminal ends) have recently been identified and characterized in chickens (Liu et al., 2007), demonstrating that avian leptin receptor gene primary transcripts are subject to similar alternative splicing events as observed previously in mammals. The

long form of the receptor is presumed to be capable of full signaling in response to bound leptin, while the physiological functions of truncated (short) forms, if any, remain to be determined (Liu et al., 2007). Sequence analysis of the putative leptin-binding domain indicates that avian leptin receptors are capable of binding mammalian leptin proteins because of their conserved structure (Richards and Poch, 2003; Niv-Spector et al., 2005). Similarly, the leptin-binding domain of the human leptin receptor has recently been shown to bind nonhuman leptin proteins, including recombinant chicken leptin (Sandowski et al., 2002). This may help explain the reported effectiveness of mammalian recombinant leptin proteins (viz., human and sheep) in reducing feed intake when administered to chickens (Denbow et al., 2000; Taouis et al., 2001). Based on these findings, it is clear that birds express a functional leptin receptor in CNS and peripheral tissue sites.

CENTRAL AND PERIPHERAL CIRCUITS

The coordinate regulation of feed intake and energy expenditure to achieve energy balance responds to external environmental cues (feed availability, feed composition, photoperiod, temperature, stressors) and internal physiological signals (hormones, energy stores, and nutrient and metabolite levels). The brain plays a pivotal role in the process of integrating all of this information and generating appropriate responses. A distributed neural network for the control of feed intake and energy expenditure has been proposed that involves a central processor (hypothalamus) and multiple negative feedback parallel processing loops (Woods et al., 1998; McMinn et al., 2000; Blevins et al., 2002; Berthoud, 2002). The genes encoding neuropeptides and their respective receptors, expressed in hypothalamic neurons, as well as in peripheral tissues, are fundamental to creating a sensing and signaling network that forms the basis for the regulation of feed intake and energy expenditure.

Figure 2 depicts a proposed regulatory system for birds that integrates signals from peripheral tissues with specific brain centers to bring about short-term changes in appetite and long-term changes in energy expenditure that work together to maintain BW. Signals coming from the periphery include peptide hormones secreted by the gastrointestinal tract, adipose tissue, liver and pancreas, as well as neural inputs (e.g., vagal afferents). Within the brain, the brainstem contains regions, such as the so-called satiety center, that receive and process signals from vagal afferent nerves and relay signals back to the gastrointestinal tract via vagal efferents that control peripheral tissue functions and produce a sense of satiety. Cholecystokinin, a potent inhibitor of feeding, has been well studied in birds, as has bombesin and its related peptides (Denbow, 1994; Kuenzel, 1994; Jensen, 2001; Furuse, 2002). Not only does cholecystokinin stimulate gastric emptying and the release of pancreatic enzymes to aid in the digestion of feed, but it also functions as a satiety signal to the brainstem capable of depressing appetite. The importance of the gut-brain axis is reflected in a dual role demonstrated by many of the gut-derived peptide signals acting as hormones and as neuropeptides (Chaudhri et al., 2006). Their effects are relatively short-lived, and components of these signaling systems are expressed in the gut and in the brain. Moreover, because their effects on appetite generally are short-lived, gut peptide signals are not thought to play a significant role in mediating long-term changes in energy balance and BW.

Adaptive changes in feed intake and energy expenditure over the long-term contribute to homeostatic control of body energy stores and the maintenance of a constant BW. In addition to meeting immediate energy demands, feed intake can be adjusted to ensure that energy and nutrients are stored in anticipation of periods of high demand or periods of feed shortage. The hypothalamus contains multiple peptidergic neuronal circuits that are involved in the regulation of feed intake and energy expenditure. These circuits can be divided into 2 basic categories, anabolic and catabolic (Woods et al., 1998). The central melancortin system, consisting of a collection of neurons that express NPY and agouti-related peptide (**AgRP**) and a second set that express POMC, is one of the best characterized neuronal pathways involved in the regulation of feed intake and energy expenditure (Cone, 2005). Stimulation of NPY/AgRP-expressing (anabolic) neurons mediates a net increase in energy intake and storage, whereas stimulation of the POMC-expressing (catabolic) neurons results in a net decrease in energy intake and storage. Thus, the balance in the activity of these 2 circuits within the hypothalamic melanocortin system is ultimately what determines energy status and BW (Figure 2).

In mammals, changes in the circulating level of leptin and most likely insulin signal the hypothalamus to effect long-term changes in energy balance by activating and/or inhibiting specific anabolic and catabolic pathways (Schwartz et al., 2000; Woods et al., 2006). It has been suggested that αMSH acting through the melanocortin-4 receptor subtype (**MC4-R**) serves as an important central mediator for leptin action on feed intake and energy expenditure (Forbes et al., 2001). Leptin, signaling through the leptin receptor, enlists the response of POMC-expressing hypothalamic neurons that produce αMSH, which signals through MC4-R. Dridi et al. (2005) reported that leptin acts on the melanocortin system within the hypothalamus, directly or indirectly, to regulate feed intake in chickens. It is not known if circulating insulin levels reflect adipose tissue size (i.e., energy stores) in birds as seems to be the case in mammals (Woods et al., 1998; McMinn et al., 2000; Blevins et al., 2002; Woods et al., 2006). Although insulin receptors have been identified in the brain of chickens (Simon and Leroith, 1986), there are no reports of the effects of central administration of insulin on feed intake in birds (Kuenzel, 1994). However, there is evidence for elevated circulating insulin levels in fed or feed-deprived chickens with lesions of the ventromedial hypothalamus, sug-

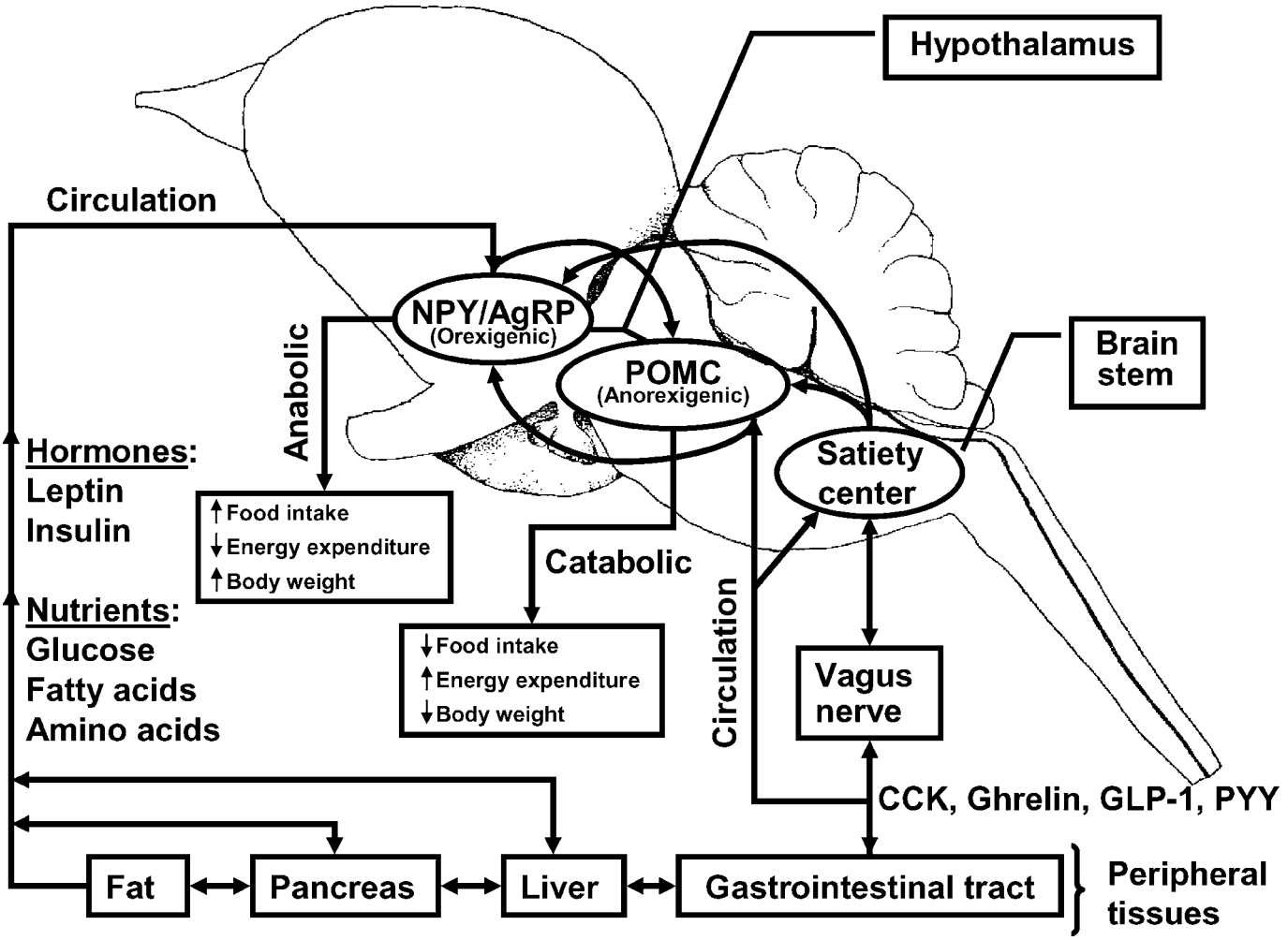

Figure 2. A proposed model describing the long-term regulation of appetite and energy balance to achieve a stable BW in poultry that integrates peripheral tissue and central nervous system circuits regulated by hormonal, neural, neuroendocrine, and nutrient signaling mechanisms. NPY = neuropeptide Y; AgRP = agouti-related peptide; POMC = proopiomelanocortin; CCK = cholecystokinin; GLP-1 = glucagon-like peptide 1; PYY = Peptide YY.

gesting the production of metabolic obesity (Sonoda, 1983). Because plasma levels of leptin and insulin rise and fall with increases and decreases in energy state in chickens such as during fasting and refeeding (Figure 3A), it is possible that these 2 key metabolic hormones could serve as peripheral signals of energy state in birds as they have been postulated to do in mammals (Niswender et al., 2004; Woods et al., 2006). In doing so, they would be expected to modulate hypothalamic melanocortin neural circuits that produce appropriate changes in feed intake and energy expenditure to achieve energy balance and maintain BW (Figure 3B).

Chickens, like mammals, express genes encoding neuropeptides such as NPY, AgRP, and POMC that form anabolic and catabolic peptidergic neuronal effector circuits in the hypothalamic melanocortin system. The NPY gene has been cloned and sequenced in chickens, and its expression in specific regions of the brain has been confirmed (Blomqvist et al., 1992; Wang et al., 2001). The NPY gene expression in the hypothalamus of birds responds to changes in energy status caused by fasting and feed restriction (Boswell et al., 1999, 2002). Moreover, NPY has been shown to be a potent orexigenic agent in chickens when administered centrally (Kuenzel et al., 1987; Kuenzel and McMurtry, 1988). Specific NPY receptors (Y1 and Y5) have been reported to mediate NPY effects on feeding behavior in chickens (Holmberg et al., 2002). The POMC gene has been identified and sequenced in chickens, and the encoded precursor protein was shown to produce bioactive αMSH that appears to play an important role in regulating feed intake in chickens (Takeuchi et al., 1999; Gerets et al., 2000; Kawakami et al., 2000). Central administration of αMSH strongly inhibits feed intake in chickens (Kawakami et al., 2000). Not only are melanocortin receptors expressed in central sites, but they are also widely expressed in peripheral tissues of chickens as well (Takeuchi and Takahashi, 1998; Boswell and Takeuchi, 2005). The AgRP gene homologue has been identified, cloned, and sequenced in chickens, and expression of this naturally occurring antagonist of melanocortin action was reported to be widespread in central and peripheral tissues

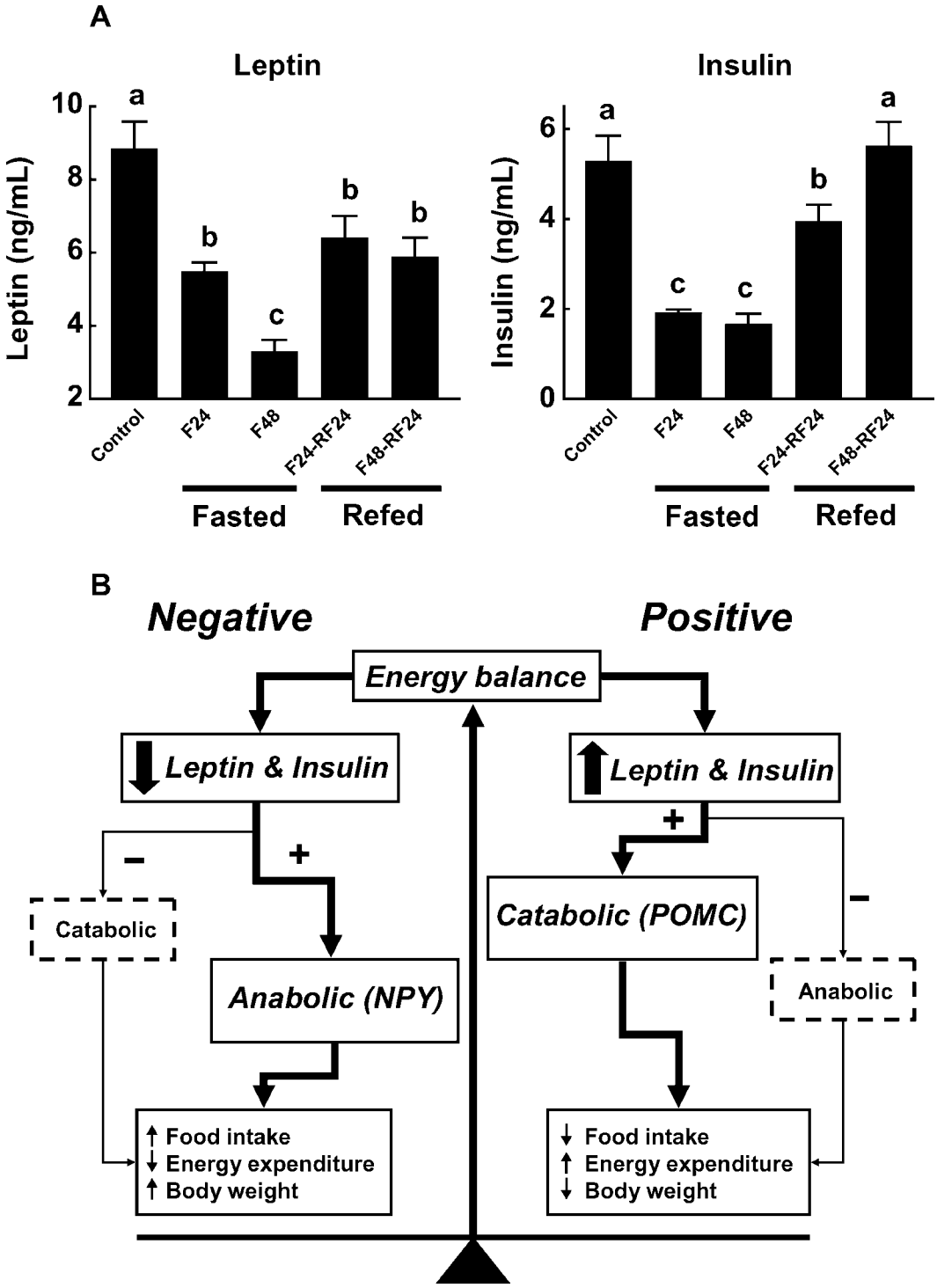

Figure 3. A) Changes in plasma leptin and insulin in 3 wk-old male broiler chickens subjected to a fast of 24 (F24) or 48 (F48) h (negative energy balance) or refed for 24 h (RF24) following a prior period of fasting (positive energy balance). Values represent the mean ± SEM. [a–c]Different letters denote statistically significant differences ($P < 0.05$). B) A proposed role for leptin and insulin as signals of energy status in birds. Two sets of hypothalamic neural circuits, orexigenic [neuropeptide Y (NPY)/agouti-related peptide-expressing] or anorexigenic [proopiomelanocortin (POMC)-expressing], are activated or inactivated in response to changes in circulating leptin and insulin. Leptin and insulin represent potential energy sensing signals to the hypothalamus that determine the appropriate level of activity in the anabolic and catabolic pathways. Acting together, these important negative feedback circuits help ensure stability in BW over the long-term.

(Takeuchi et al., 2000). The AgRP serves as an antagonist of αMSH in chickens, as it does in mammals, by binding to specific melanocortin receptor subtypes (MC3-R and MC4-R). Furthermore, AgRP is upregulated, like NPY, in response to fasting (Phillips-Singh et al., 2003). The AgRP is orexigenic in layer-type chickens, but not broilers, when administered centrally (Tachibana et al., 2001). Based on these observations, it was concluded that the MC4-R might function in the regulation of feed intake and energy expenditure in chickens (Tachibana et al.,

2001; Boswell and Takeuchi, 2005) as this particular receptor subtype has been postulated to do in mammals and that the central melanocortin system appears to be well conserved between birds and mammals (Phillips-Singh et al., 2003).

ADENOSINE MONOPHOSPHATE-ACTIVATED PROTEIN KINASE: AN ENERGY SENSOR

Nutrient (fuel) and metabolite sensing pathways within hypothalamic neurons represent another set of regulatory mechanisms that work to bring about changes in whole body energy balance. One such example involves adenosine monophosphate-activated protein kinase (**AMPK**), a highly conserved energy sensor that also regulates cellular metabolism (Hardie et al., 2003; Carling, 2004). Adenosine monophosphate kinase is a serine/threonine kinase and a central component of a kinase-signaling cascade that is a critical control point for maintaining cellular energy homeostasis (Hardie, 2004; Carling, 2005; Kahn et al., 2005; Hardie et al., 2006). It is a heterotrimeric enzyme complex that consists of 1 catalytic (alpha) and 2 regulatory (beta and gamma) subunits. Adenosine monophosphate kinase is an energy-sensing enzyme that is activated by metabolic and environmental stresses that deplete cells of energy (adenosine triphosphate). In response to changes in the AMP/ATP ratio, AMPK is activated by phosphorylation via an upstream kinase (AMPK kinase) such as the tumor suppressor protein LKB1 or the calcium/calmodulin-dependent protein kinase kinase. Activation of AMPK inhibits ATP-consuming anabolic pathways and stimulates ATP-producing catabolic pathways in an attempt to restore cellular energy charge (Figure 4). This is accomplished by regulating the activity and expression levels of key metabolic enzymes involved in lipid, carbohydrate, and protein metabolism, as well as other related cellular pathways.

The level of metabolic flux through the fatty acid biosynthetic pathway in hypothalamic neurons as regulated by AMPK determines the levels of 2 key metabolites, malonyl-CoA, and long chain fatty acyl-CoA that, in turn, lead to changes in feed intake and energy expenditure by altering the expression of orexigenic and anorexigenic neuropeptides in melanocortin system neurons (Lane et al., 2005; Lam et al., 2005; He et al., 2006). The AMPK inhibits the activity of acetyl-CoA carboxylase, the rate-limiting enzyme involved in the production of malonyl-CoA used for fatty acyl-CoA biosynthesis, and causes a reduction in this reaction. It also stimulates the activity of malonyl-CoA decarboxylase that catalyzes the conversion of malonyl-CoA to acetyl-CoA. Malonyl-CoA inhibits the activity of carnitine palmitoyl-CoA transferase-1, a transport protein located in the inner mitochondrial membrane that governs the uptake of fatty acyl-CoA into the mitochondria for oxidation which, in turn, affects the steady state level of long chain fatty acyl-CoA. Thus, malanonyl-CoA and long chain fatty acyl-CoA serve as indicators of energy status in the hypothalamus where they trigger reduced expression of orexigenic neuropeptides (NPY/AgRP) and increased expression of anorexigenic neuropeptides (POMC) within hypothalamic neurons (Hu et al., 2003; Lane et al., 2005). This concept has been referred to as the malonyl-CoA hypothesis, which postulates that increased levels of malonyl-CoA, indicative of an elevated energy status, inhibit feed intake and BW gain (Dowell et al., 2005). Because the fatty acid biosynthetic pathway is also active in the hypothalamus, the key metabolites (malonyl-CoA and long chain fatty acyl-CoAs) serve as signals of energy status to the anorexigenic (POMC-expressing) and orexigenic (NPY/AgRP-expressing) neuronal circuits of the melanocortin system that control feed intake and peripheral energy expenditure (Lane et al., 2005).

The hormones leptin and insulin inhibit AMPK in the hypothalamus (Minokoshi et al., 2004; Carling, 2005). This leads to increased activity of acetyl-CoA carboxylase, which results in an increased level of malynoyl-CoA. Elevated malonyl-CoA promotes anorexigenic signaling, which reduces feed intake and increases energy expenditure (Wolfgang and Lane, 2006). The AMPK also functions in peripheral tissues such as liver and skeletal muscle to bring about changes in energy balance (Carling, 2004; Kahn et al., 2005). Thus, the coordinated regulation of hypothalamic AMPK and its downstream actions on metabolic pathways plays a critical role in integrating hormonal and nutrient signaling that affects feed intake and whole-body energy homeostasis.

Recently, we have begun to explore aspects of the AMPK signaling pathway in chickens (Proszkowiec-Weglarz et al., 2006a,b). Seven AMPK subunit genes have been identified and their expression studied in different tissues including the hypothalamus. Genes for 2 upstream AMPK kinases, LKB1 and calcium/calmodulin-dependent protein kinase kinase, have also been identified in chickens and their expression investigated (Proszkowiec-Weglarz et al., 2006b; Proszkowiec-Weglarz and Richards, unpublished findings). Active (phosphorylated) AMPK has been detected in peripheral tissues as well as in hypothalamic feeding centers, suggesting the existence of a functional AMPK pathway in birds with similar characteristics to mammals (Proszkowiec-Weglarz et al., 2006b). However, the precise role(s) of the AMPK pathway in regulating feed intake and energy expenditure in birds and the specific signaling mechanisms involved remain to be fully elucidated.

HYPOTHALAMIC INTEGRATION OF NUTRIENT AND HORMONAL SIGNALING

A novel concept has recently emerged that defines specific neuronal subpopulations in the hypothalamus capable of integrating signals from hormones such as leptin and insulin with fuel (nutrient) sensing mechanisms leading to adjustments in feed intake and energy expenditure mediated via kinase signaling pathways. In

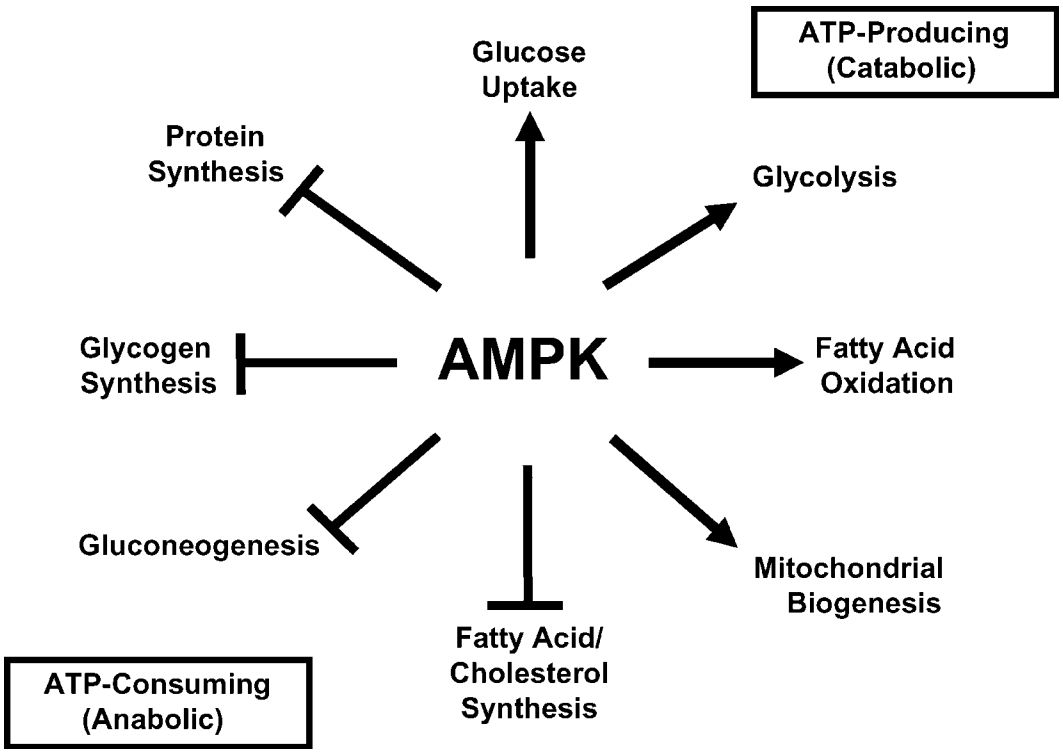

Figure 4. Key metabolic pathway activities that are regulated by adenosine monophosphate-activated protein kinase (AMPK). Arrows designate pathways that are stimulated by AMPK [adenosine triphosphate (ATP)-producing], whereas lines with bars indicate pathways that are inhibited (ATP-consuming). Adapted from Hardie et al. (2006).

fact, a new hypothalamic fuel-sensing/signaling pathway has been proposed involving mammalian target of rapamycin (**mTOR**), a serine/threonine kinase complex that integrates cellular energy sensing with hormonal signals of peripheral energy stores in specific populations of neurons to regulate feed intake and achieve energy balance (Cota et al., 2006). The mTOR functions as a sensor of energy status and, based on information received from signaling molecules, regulates the rate of cellular protein synthesis, growth, and proliferation commensurate with nutrient availability (Wullschleger et al., 2006). Moreover, mTOR was reported to colocalize with NPY/AgRP- and POMC-expressing neurons in the arcuate nucleus of rat hypothalamus (Cota et al., 2006). Elevated cellular ATP increases mTOR activity, and this could indicate that mTOR may also act as an ATP sensor. Central administration of specific nutrients such as the branched chain amino acid leucine activates mTOR signaling that leads to decreases in feed intake and BW (Cota et al., 2006).

A number of hormones and cytokines linked to energy signaling pathways mediate their effects through mTOR (Wullschleger et al., 2006). Leptin was found to increase hypothalamic mTOR activity via the signal transducer STAT3, a product of signaling through the leptin receptor (Cota et al., 2006). Conversely, inhibition of mTOR signaling by administration of rapamycin antagonizes leptin's inhibitory effect on feed intake. Moreover, mTOR activity is increased in response to insulin and insulin-like growth factor binding to their respective receptors that, in turn, activate the PI3K/Akt signal transduction pathway (Wullschleger et al., 2006). Thus, mTOR serves as a fuel sensor and, when active in the hypothalamus, this signaling pathway has direct effects on reducing feed intake and BW while increasing energy expenditure (Cota et al., 2006).

Like AMPK, mTOR responds to changes in energy status; however, unlike AMPK, mTOR is activated (phosphorylated) in response to elevated energy status (Wullschleger et al., 2006; Cota et al., 2006). Activation of AMPK-dependent pathways leads to the inactivation of mTOR (Hardie, 2004). Thus, in the hypothalamus, as well as in peripheral tissues, AMPK and mTOR have overlapping but reciprocal functions (Cota et al., 2006). Figure 5 depicts a proposed hypothalamic regulatory model that involves input signaling from nutrients and hormones that influence AMPK activity, which affects malonyl-CoA levels (malonyl-CoA hypothesis) and TOR signaling via its effects on protein synthesis and cell growth to bring about changes in the expression of orexigenic and anorexigenic neuropeptides and thus modulate the activity of melanocortin system neural circuits. The net activity of these 2 opposing pathways ultimately determines a metabolic balance that leads to changes in feed intake and energy expenditure mediated by the actions of orexigenic and anorexigenic neural circuits. The TOR gene homologue, located on chromosome 21, is widely expressed in chicken tissues, including in the hypothalamus (M. Proszkowiec-Weglarz and M. P. Richards, unpublished findings). Although the existence and

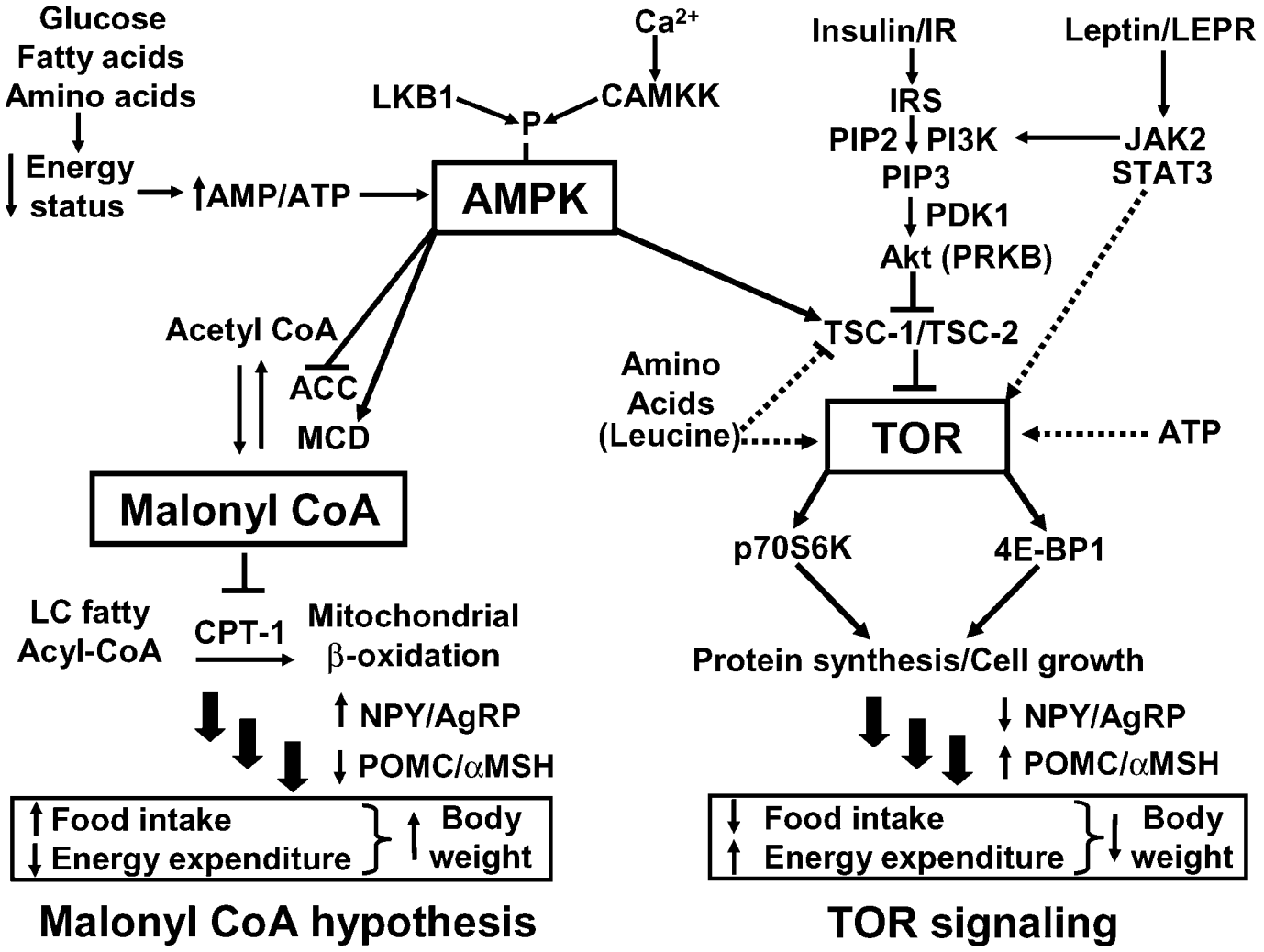

Figure 5. A proposed model depicting the integration of nutrient, metabolite, and hormonal signaling by the combined actions of the adenosine monophosphate (AMP)-activated protein kinase (AMPK) and target of rapamycin (TOR) pathways within hypothalamic neurons to regulate feed intake, energy expenditure, and BW. LKBI = Ser/Thr kinase 11, also known as STK11; CAMKK = Ca/calmodulin-dependent protein kinase kinase; ATP = adenosine triphosphate; ACC = acetyl-CoA carboxylase; MCD = malonyl-CoA decarboxylase; CPT-1 = carnitine palmitoyl-CoA transferase-1; NPY = neuropeptide Y; AgRP = agouti-related peptide; POMC = proopiomelanocortin; αMSH = α-melanocyte stimulating hormone; IR = insulin receptor; IRS = insulin receptor substrate; PIP2 = phosphatidylinisitol 4,5-bisphosphate; PIP3 = phosphatidylinisitol 3,4,5-triphosphate; PI3K = phosphatidylinisitol-3 kinase; PDK1 = phosphoinositide-dependent protein kinase 1; PRKB = protein kinase B, also known as Akt; TSC-1 = tuberous sclerosis protein 1; TSC-2 = tuberous sclerosis protein 2; p70S6K = 70 kDa-ribosomal protein S6 kinase; 4E-BP1 = eukaryotic initiation factor 4E-binding protein 1; LEPR = leptin receptor; JAK2 = janus knase 2; STAT3 = signal transducer and activator of transcription 3.

functioning of a hypothalamic TOR signaling pathway in birds has yet to be demonstrated, the Akt/TOR/p70S6K pathway has recently been characterized in chicken muscle that is stimulated by insulin and refeeding and was found to function in the nutritional regulation of mRNA translation and protein synthesis (Duchene et al., 2006; Tesseraud et al., 2006).

CONCLUSIONS AND FUTURE DIRECTIONS

Much progress has been made during the past decade concerning the identification and characterization of signaling and regulatory pathways that govern feeding behavior and energy expenditure in animals. Although less is known about avian species, advances are being made in defining the control of energy balance at the gene and molecular levels. The critical role of hypothalamic melanocortin system feeding circuits and their functioning are well conserved between birds and mammals, although some of the many input-signaling pathways like ghrelin may function differently. A number of new concepts have emerged recently such as fuel sensing, kinase signaling pathways, regulatory roles of nutrients and metabolic substrates, and the intermediary roles of intracellular signal transduction cascades on regulating feed intake and energy expenditure integrated by specific subpopulations of hypothalamic neurons. These areas have been the subjects of ongoing investigation primarily in mammalian model systems. Exploring such concepts in poultry will undoubtedly add to our understanding of the control of feed intake and energy expenditure in these species and serve to guide future research in this area. However, despite the many apparent simi-

larities, it would be incorrect to assume that all of these findings will be directly applicable to poultry species. The challenge for the future remains to better define the molecular basis for the intricate and highly interconnected mechanisms, both common and unique, governing feed intake, energy expenditure, and BW regulation in poultry.

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